Specialty Conference

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Treatment of Peptic Ulcer Disease — A Symposium

JAMES H. MEYER, MD:* Peptic ulcer disease remains an important source of morbidity and absenteeism and, consequently, economic loss to our society. The causes of ulcer disease are unclear, but diseases with poorly understood causes can be effectively treated on an empiric basis. We are here today to assess current treatment of ulcer disease.

To begin this discussion, Dr. Schwabe will describe conventional ulcer treatment. Dr. Isenberg will then try to assess for us the effectiveness of this therapy. Next, Dr. Sturdevant will summarize available information on promising, new pharmacotherapies. Dr. Grossman, Dr. Passaro and I will then discuss aspects of surgical treatment of ulcer disease.

ARTHUR SCHWABE, MD:† Factors implicated in the development of peptic ulceration are excessive and prolonged secretion of acid and pepsin and impaired mucosal resistance. Conventional ulcer therapy is designed to reduce the amount of acid in the stomach by neutralization, buffering or inhibition of secretion. The goals of this therapy are (1) to alleviate ulcer symptoms, (2) to promote ulcer healing and (3) to prevent complications and recurrence. To accomplish these goals antacids, anticholinergics and specialized diets are commonly used.

Antacids

Antacids have achieved wide acceptance by both patients and doctors as the single most effective and rational form of ulcer therapy. More than $100 million is spent each year in the United States for the purchase of antacids. Most patients with pain from an acute ulcer obtain prompt relief from 30 ml of liquid antacid, equivalent to about 60 mEq of neutralizing capacity.[1] However, scientific proof of antacid efficacy in achieving the goals of ulcer therapy is incomplete.

Increasing awareness of the pharmacology of antacids has led to the concept of tailoring the antacid to a patient's requirements and tastes.[1,2] Factors such as buffering capacity and duration of action determine dosage schedules. Relative cost, palatability, sodium content and side effects additionally are considered in the selection of one of many available antacid preparations for a given patient.

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ABBREVIATIONS USED IN TEXT
dm E_2 = 16, 16-dimethyl prostaglandin E_2
TDB = tri-potassium di-citrato bismuthate

The buffering effect of antacids in the fasting state lasts approximately 30 minutes. However, following a meal this buffering effect is prolonged to three to four hours. Liquid antacids are more effective buffers than antacid tablets. Although potent buffers, calcium-containing antacids increase gastric secretion after their buffering effect has subsided[3,4] and may also produce elevations in serum calcium, creatinine, phosphorus and bicarbonate. For these reasons, calcium-containing antacids cannot be recommended for ulcer management.

The above considerations underlie what we prescribe for patients with gastric or duodenal ulcer (Table 1), which is not far different from what most gastroenterologists advise.

Anticholinergics

The use of anticholinergics in the management of peptic ulcer is based on the observations that they reduce basal, nocturnal and stimulated gastric acid secretion. They may also prolong the duration of antacid action by keeping antacid in the stomach longer.

The desired antisecretory effects of anticholinergics are invariably accompanied by predictable side effects, such as dry mouth and constipation. When a decision is made to use one of these agents, the dose has to be titrated to a level just below that which produces these side effects. The optimum effective dose varies with each individual patient, with the type of preparation and with the time of administration. The duration of action of these drugs is greatest when taken after a meal. Absolute and relative contraindications of anticholinergics are listed in Table 2.

Because of the narrow margin between desired and untoward effects and occasional severe complications, anticholinergics have lost much of their popularity in standard ulcer therapy. They are most effective if given at bedtime for reduction of nocturnal acid secretion and nighttime pain.

TABLE 2.—*Anticholinergics in Treatment of Peptic Ulcer*

Absolute Contraindications
Gastric retention
Glaucoma
Prostatism
Pulmonary disease (chronic)
Relative Contraindications
Constipation
Central nervous system symptoms
Esophageal reflux
Impotence
Hot climates (anhidrosis)
Old age

Diet

A bland or restrictive diet has traditionally been an accepted component of conventional ulcer therapy. The precise composition, caloric content and number of feedings of these ulcer diets vary. In some of these diets it is presumed that dark meat, dark bread, spices, raw fruits and uncooked vegetables aggravate or perpetuate an ulcer and are therefore contraindicated. Consequently the use of milk, cottage cheese, white fowl meat, rice, mashed potatoes and vegetables prepared in a blender is stressed. Although as a rule these diets are monotonous and unpalatable, most patients readily accept, or may even request, dietary restrictions.

A brief review of our current knowledge of the physiologic effect of the different dietary constituents on gastric secretion is in order. A standard meal has been shown to neutralize gastric contents for 30 to 60 minutes and is then followed by increased acid secretion and an increase in gastric acidity.[5] Constituents of foods vary in their buffering capacity and in their ability to stimulate acid secretion. The immediate effect of food protein is to buffer gastric acid, but this is followed by active stimulation of gastric secretion. The net

TABLE 1.—*Guidelines for Antacid Therapy*

Type: Mixtures of aluminum hydroxide; magnesium hydroxide; magnesium trisilicate

	Dosage	*Frequency*	*Maintenance Rx*
Gastric Ulcer	40 mEq (15-20 ml)	Every hour for 12 weeks*	1-3 hours after meals and on retiring; indefinitely†
Duodenal Ulcer	75-100 mEq (30-60 ml)	Every hour for 2 weeks	1-3 hours after meals and on retiring; for 6 weeks

*Ulcer must show signs of healing after 3 weeks.
†If ulcer has completely healed.

effect of a protein meal is to increase the load of acid delivered to the duodenum. Although fats and carbohydrates cause less stimulation of acid secretion, they have little or no buffering capacity. Fruit juices contain a significant amount of buffer and tend to maintain a pH near their own level. Pepper in the absence of food may produce gastric hyperemia and edema, but there is no evidence that it causes peptic ulceration. Evidence that other spices cause peptic ulcer is nonexistent. Caffeinated beverages have been clearly shown to stimulate gastric secretion. Alcohol does not stimulate acid secretion, but may produce gastritis.

There is no evidence that a bland diet is of any benefit in ulcer management.[6] Other time-honored concepts, such as hourly administration of milk and cream, multiple feedings and the bedtime snack, have been shown to induce a net increase in the acid load and have been abandoned.

For patients with peptic ulcer, there should be dietary restrictions on alcohol, caffein-containing beverages and aspirin. Finally, patients should be encouraged to eat three nutritious, enjoyable meals of their own choosing every day.

JON I. ISENBERG, MD:* Does conventional ulcer therapy, as outlined by Dr. Schwabe, really work? Probably not, but we really do not know. The reasons for this uncertainty are related to the following factors which make therapeutic studies in peptic ulcer difficult. First, ulcer disease waxes and wanes spontaneously. Therefore, a spontaneous cure may be confused with a therapeutic cure. Consequently, only large and carefully controlled studies can show therapeutic efficacy. Second, only recently have studies been directed at determining the natural history of ulcer disease using endoscopy to quantitate healing rate. Most of the earlier studies used x-ray examination, which is notoriously inaccurate in quantitating the size of duodenal ulcers. Third, as is the case with many clinical studies, criticisms can be made regarding experimental design. Factors such as double-blindedness, randomization, use of a satisfactory placebo and the like were often not taken into account in many of the earlier studies.

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Antacids

The mainstay of ulcer therapy over the past 20 centuries has been antacids. Pliny in the first century AD was reported to have used crushed coral, chalk, to relieve abdominal pain. Paracelsus, in the 16th century, used powdered pearls, somewhat more costly than antacids. Others followed suit with minor variations on the theme; Rokitansky adding milk and alkaline powders. With such a strong tradition, it is difficult to question the role of antacids in ulcer therapy. Also, the use of antacids seems to make good sense: (1) ulcers do not form in the absence of acid and antacids reduce both acidity and peptic activity, (2) antacids prevent the formation of experimental ulcers in animals and (3) surgical therapy, which usually cures ulcers, is thought to produce its effect by decreasing acid and pepsinogen secretion.

Now let us examine the effectiveness of antacids. We need to know (1) whether antacids

TABLE 3.—*Effects of Antacids or Placebos on Ulcer Pain*

	Blind	Test Agent	Ulcer	Results
Placebo alone				
1936 Flood and Mullins[6]	o	Histidine vs saline	DU	8/12 saline relief, 4/6 hist. relief,
1947 Gill[7]	o	Sterile water	GU	19/20 relief
Antacid vs Placebos				
1947 Smith[8]	o	Reactive vs non-reactive aluminum hydroxide	DU	No difference in 63 patients
1952 Lawrence[9]	o	Barium vs aluminum hydroxide, magnesium carbonate, magnesium trisilicate	DU, GU	Magnesium better than barium or aluminum
1973 Hollander, Harlan[11]	+	Calcium carbonate vs placebo tablet	DU, GU	No difference DU, AA effect in GU
1975 Butler, Gersh[12]	+	Aluminum + magnesium AA vs placebo	GU	No difference
1976 Sturdevant et al[13]	+	Aluminum + magnesium AA vs placebo	GU	No difference

o indicates nonblinded study
+ indicates double-blind
DU indicates duodenal ulcer
GU indicates gastric ulcer
AA indicates antacid

relieve ulcer pain (Table 3) and (2) whether antacids promote ulcer healing (Table 4) as compared with inactive, placebo agents.

In 1936, Flood and Mullins[6] reported that daily parenteral injections of saline produced relief in 8 of 12 symptomatic outpatients with duodenal ulcers within a few days. Gill[7] in 1947 reported that injection of distilled water resulted in pain relief in 19 of 20 patients with gastric ulcers and that ulcer healing occurred over four to eight weeks as determined gastroscopically. Both studies failed to contrast the responses to that produced by conventional therapy (this is, admission to hospital, changes in diet, use of antacids, cessation of smoking and so forth), but both studies suggested that ulcer pain is responsive to placebo effects.

Comparisons between inert placebos and antacids began in 1947 (Table 3). Smith[8] reported a reactive liquid aluminum hydroxide antacid tablet relieved pain no more effectively than a nonreactive aluminum hydroxide tablet which probably had little, if any, buffering effect. Lawrence[9] examined the effect of serial doses of liquid barium sulfate (placebo) with aluminum hydroxide and magnesium carbonate or magnesium trisilicate in 108 patients with either gastric or duodenal ulcers. The magnesium-containing antacids were superior to either barium or aluminum hydroxide in producing pain relief. Of the magnesium treated patients there was either partial or complete pain relief in 85 percent, while relief occurred in about 50 percent of the patients treated with barium sulfate and aluminum hydroxide. Palmer[10] reported that of 230 patients in hospital, 106 preferred aluminum hydroxide antacid, 93 preferred diluted hydrochloric acid and 31 had no particular preference as to which of the two agents produced greater relief of ulcer pain.

While these studies compared pain relief from antacids with that from placebos, they were not blind studies, and results were conflicting among the studies. Double-blind comparisons have been made only recently.

Three double-blind prospective studies have examined the effect of antacid versus placebo in relieving ulcer pain. Hollander and Harlan[11] contrasted the effect of calcium carbonate plus glycine tablets in both patients with gastric ulcers and those with duodenal ulcers. In the patients with gastric ulcers, antacid was found to be superior to placebo in relief of ulcer pain: all antacid-treated patients were pain-free after 30 days of treatment, while only 50 percent of the placebo-treated patients were pain-free. In the patients with duodenal ulcers, antacids tended to be superior to placebo in relief of ulcer symptoms, but the differences were not statistically significant. Butler and Gersh contrasted 30 ml of a liquid antacid with placebo in inpatients with gastric ulcers. They claim[12] that all of their patients were pain-free within 72 hours of admission to hospital. There were no distinct differences between those treated with antacid and those treated with placebo. Sturdevant and associates[13] have attempted to determine if single doses of antacid differ from placebo in relief of symptomatic duodenal ulcer pain. They conducted two studies; one with patients in hospital and the second largely with outpatients. The inpatients received serial doses of antacid or placebo for pain over five days and recorded their pain relief. The second group was carefully evaluated in five-minute intervals for 30 minutes after ingestion of antacid or placebo for two separate episodes of pain. There were no differences in time of onset of pain relief, duration of pain relief or degree of pain relief. *Taken together these results suggest that antacids are probably not notably different from a liquid placebo in relief of ulcer pain.*

Now to turn to the question "Do antacids expedite healing?" (Table 4). Sir Richard Doll and his associates at the Central Middlesex Hospital, London,[14] were the first group to evaluate carefully a number of treatment programs in ulcer patients. Their patients were randomly assigned to type of treatment, and in some cases a placebo was used, but the studies were not blind. Radiography was used as the measure of gastric ulcer healing. They studied a number of therapeutic approaches and agents simultaneously (such as ascorbic acid, phenobarbital, hospital admission, belladonna and sodium bicarbonate plus milk drip). They observed that a six pint per day milk drip plus 40 grams of sodium bicarbonate did not alter gastric ulcer healing when contrasted to a control group not receiving the milk drip.

Baume and Hunt[16] found that healing of gastric ulcers in outpatients was no different in those treated hourly with calcium carbonate powder when contrasted to those treated with an inactive aluminum hydroxide tablet over a three week period. In fact the mean decrease in ulcer size

at three weeks was less in those who received calcium carbonate (29 percent) than those who received the inactive aluminum preparation (56 percent).

Using endoscopy for measuring, Hollander and Harlan reported that in their antacid-treated gastric ulcer group there was more ulcer healing than in a placebo-treated group. However, Butler and Gersh[12] were not able to confirm these findings in 28 patients in hospital with gastric ulcers who were randomly assigned for liquid antacid or placebo administration. They observed that in 11 of 15 antacid-treated and in 10 of 13 placebo-treated patients there was at least 67 percent healing after three weeks in hospital.

In summary, antacids are probably no more effective than placebo in ulcer healing. Possible reasons for their lack of efficacy include poor patient compliance, transient buffering effect and factors other than acid or peptic activity which influence ulcer healing.

Should we continue to prescribe antacids for patients with ulcers? I think that we should because they are the current standard of practice. If additional studies fail to show a distinct efficacy, their future use may be curtailed.

Anticholinergics

Unfortunately, the story regarding the efficacy of anticholinergics is no clearer than the antacid tale. Although approximately $65 million is spent each year for anticholinergics, we remain uncertain that they are of proven efficacy in expediting ulcer healing, relieving pain or decreasing the frequency of complications or recurrences. The same difficulties are encountered in evaluating these agents as in evaluating the effectiveness of antacids. In addition, the anticholinergic saga is compounded by the difficulty of designing blind studies for testing the drugs because anticholinergics have inherent nongastrointestinal side effects (such as dryness of the mouth, blurred vision and urinary retention).

A large number of studies have been directed at determining whether anticholinergics are superior to placebo in the relief of ulcer recurrences or complications (Table 5). Those in which a fixed dose of anticholinergics has been used probably should not be given much weight, because it is well known that in order for anticholinergics to effectively inhibit acid secretion they should be prescribed at an individually determined optimal effective dose (that is, the dose one increment less than that which produces significant side effects).

Most (9 of 12) of the studies failed to document the effectiveness of anticholinergics in preventing ulcer recurrences and complications. Sun[21] and Sun and Ryan[22] claimed that there were fewer ulcer recurrences in patients with duodenal ulcers treated with anticholinergics when compared with a placebo-treated group, but complications occurred with almost equal frequency in the two groups. Amure's[23] results in patients with duodenal ulcers studied in Nigeria are difficult to evaluate because the superiority of anticholinergics versus placebo was related primarily to chronic vomiting in 97 percent of the placebo-treated groups, whereas, chronic vomiting is not frequently encountered among groups of ulcer patients in our society.

Three studies deserve brief comment. Walan[24] reported that there were significantly fewer recurrences and complications with less time lost from work over a two-year period in a group of 29 patients with duodenal ulcers treated with anticholinergics versus those receiving placebo. However, this was not a blind study and it is difficult to determine if biases might have influenced the findings. Baume and Hunt[25] reported greater gastric ulcer healing in inpatients and fewer gastric ulcer recurrences in outpatients treated with anti-

TABLE 4—*Effectiveness of Antacid on Ulcer Healing*

		Blind	*Test Agent*	*Ulcer*	*Results*
1956	Doll et al[15]	o	Multiple agents, milk + HCO_3	GU	No effect of milk + HCO_3 vs no treatment
1969	Baume, Hunt[16]	±	$CaCO_3$ vs inert AlOH tablet	GU	No difference in outpatient healing
1973	Hollander, Harlan[11] ..	+	$CaCO_3$ vs placebo tablet	GU	Effective in GU No effect in DU
1975	Butler, Gersh[12]	+	Aluminum + magnesium AA vs placebo	GU	No difference

o indicates unblinded
+ indicates double-blind
± indicates some degree of blindness but not truly double-blind

DU indicates duodenal ulcer
GU indicates gastric ulcer
AA indicates antacid

HCO_3 indicates bicarbonate
$CaCO_3$ indicates calcium carbonate
AlOH indicates aluminum hydroxide

cholinergics. Again, this was not a fully blind study and therefore its results are open to some question. Ruffin and Cayer[26] found that anticholinergic therapy was associated with fewer recurrences, fewer gastrointestinal hemorrhages and better clinical results than placebo in patients with duodenal ulcers treated for at least eight months.

It seems to me, *as with antacids, anticholinergics do not have a consistent therapeutic effect on peptic ulcer with respect to healing, recurrence or complications.* They may be of value, as they are often stated to be, in those patients with ulcers who have nocturnal pain, or in those who are recalcitrant to routine antacid therapy. However, their efficacy under these conditions needs to be carefully evaluated.

Finally, a brief comment on admission to hospital and discontinuation of smoking in patients with gastric ulcer. Doll and co-workers[14] reported that the healing of gastric ulcers in patients in hospital was greater than in outpatients; but these studies were confounded by the simultaneous prescription of other treatments while the patients were in hospital and therefore the conclusion must be qualified. Because the economic burden of three weeks of hospital stay is so great, most patients with gastric ulcers are admitted only for evaluation to be certain that the ulcer is benign, and then discharged. Since most gastric ulcers heal with outpatient management, this policy is certainly acceptable, provided the physician is finally able to ascertain complete healing during the course of outpatient management.

Also, Doll and associates[14] showed that discontinuation of cigarette smoking by patients produced faster gastric ulcer healing than occurred in patients whose smoking habit was unaltered. However, nonsmokers had slow rates of ulcer healing comparable to those in the continuing smokers, so the effects of abstinence from smoking were not totally clear. Moreover, Hermann and Piper[32] were not able to confirm these observations in a retrospective study; but since smoking is hazardous to one's health the use of tobacco should be curtailed.

Neither of the two major classes of drugs that have been extensively used, antacids and anticholinergics, appears to have a dramatic effect consistently and significantly greater than placebo. Clinical studies of the more potent acid-pepsin

TABLE 5—*Do Anticholinergics Really Work?*

		Number of Cases	*Blind*	*Test Agent*	*Ulcer*	*Results*
1954	Doll and Pygott[17] ...	32	o	Belladonna	GU	No difference, healing
1954	Friedlander[18]	100	o	Methantheline	DU	No difference, recurrence
1961	Melrose, Pinkerton[19] .	58	+	Poldine methylsulfate*	DU	No difference, recurrence
1961	Lennard-Jones[20]	11	±	Poldine methylsulfate*	DU	No difference, recurrence
1964	Sun[21]	37	+	Glycopyrrolate (Robinul®)*	DU	Less recurrence in treated vs placebo, equal complications
1965	Amure[23]	120	+	Glycopyrrolate (Robinul®) Propantheline bromide (Pro-Banthine®)	DU	Anticholinergics superior
1966	Hunt, Wales[27]	13	+	Poldine methylsulfate	DU	No difference, recurrence
1967	Trevino, et al[28]	46	+	Glycopyrrolate (Robinul®)*	DU	No difference, recurrence
1968	Goyal, et al[29]	60	+	Oxyphencyclimine hydrochloride (Daricon®)	DU	No difference, recurrence
1970	Sun, Ryan[22]	75	+	Propantheline bromide (Pro-Banthine®)	DU	Less recurrence in treated vs placebo, equal complications
1970	Kaye, et al[30].....	91	o	Propantheline bromide (Pro-Banthine®)* L-hyoscyamine sulfate	DU	No difference, recurrence
1970	Walan[24]	50	±	L-hyoscyamine sulfate*	DU	Less recurrence in treated
1971	Baume, et al[25]	40	±	Glycopyrrolate (Robinul®)*	GU	Greater healing in inpatient and less recurrence in treated
1972	Cocking[31]	65	o	Propantheline bromide (Pro-Banthine®)	DU	No difference, symptoms, recurrence

726 DU patients randomized
72 GU patients randomized

o indicates unblinded
+ indicates double-blind
± indicates some degree of blindness but not truly double-blind

DU indicates duodenal ulcer
GU indicates gastric ulcer

*Indicates optimal effective anticholinergic dose treated.

inhibitors (such as H_2-receptor antagonists, prostaglandins) and other agents (such as bismuth) may make important inroads toward improving ulcer therapy.

RICHARD STURDEVANT, MD:* Because the effectiveness of traditional ulcer therapy is in question, the search continues for more effective agents. Experimental drugs potentially useful in treatment of peptic ulcer include carbenoxolone; 16, 16 dimethyl prostaglandin D_2; cimetidine, and bismuth. None are available now for routine use in the United States.

Carbenoxolone is synthesized from glycyrrhetinic acid extracted from liquorice root. It nearly halves the time for healing of gastric ulcers in outpatients.[33,34] Its mechanism of action is not established. Its known effects on gastrointestinal physiology, which may be related to its ulcer healing effect, are listed in Table 6.

The recommended dose is 100 mg three times a day for one week, followed by 50 mg three times a day until the ulcer heals. The toxicity of carbenoxolone closely resembles that of excess aldosterone. With the recommended dose, about 50 percent of patients will have water retention or hypertension as side effects.[35,36] Hypokalemia is somewhat less frequent, but may be life-threatening.[37] Worsening of preexisting congestive heart failure results from sodium and water retention.

Side effects may be treated with a thiazide diuretic and potassium supplements. Antialdosterone drugs block not only the side effects, but also the therapeutic action of carbenoxolone.

Because of the side effects, structurally closely-related compounds have been tested. Of these, the most promising seems to be geranyl farnesyl acetate (Gefarnate®). This drug lacks carbenoxolone's side effects, but is less effective.[33]

Carbenoxolone is neither clearly effective in treatment of duodenal ulcers nor, when given chronically, in prevention of recurrence of gastric ulcer.

Prostaglandin E_2

16, 16-Dimethyl prostaglandin E_2 (dm E_2) is a synthetic prostaglandin which reduces gastric acid secretion when given by mouth. Some of its effects on gastrointestinal physiology are listed in Table 7. Its mechanism of inhibition of acid secretion is not established. While an effect via cyclic adenosine monophosphate (AMP) seems plausible, this has not been proven. Inhibition of acid secretion may be secondary to inhibition of gastric mucosal blood flow.[38]

TABLE 6.—*Effects of Carbenoxolone*

Increased life span of gastric epithelial cells
Increased volume of gastric mucus
Altered composition of gastric mucus
Inhibition of pepsin
Decreased back diffusion of hydrogen ion
Release of secretin into blood

TABLE 7.—*Some Gastrointestinal Effects of Prostaglandin E_2*

Decreases
Gastric acid secretion
Gastrin secretion
Gastric mucosal blood flow
Gastric emptying
Antral contraction
Colon contraction (circular muscle)
Increases
Hydrogen ion back-diffusion into gastric mucosa
Jejunal sodium and water secretion
Colon contraction (longitudinal muscle)

Dm E_2 increased the healing rate of gastric ulcers in one small trial in man.[39] No other therapeutic trials have been reported. In animals it inhibits the formation or hastens healing of ulcers or erosions in several experimental models. Dm E_2 may "break" the gastric mucosal barrier to acid back-diffusion.[40,41] Despite this observation, it is effective in rats in reducing the amount of gastric mucosal bleeding due to the "barrier-breakers"—aspirin, or aspirin and taurocholic acid together.[42]

Diarrhea occurs in some patients following administration of dm E_2 in doses for therapy.[39] The diarrhea is probably related to the secretory and motor effects of dm E_2 (Table 7).[43]

Cimetidine

Cimetidine is a synthetic compound structurally related to histamine.[44] It inhibits those effects of histamine not blocked by conventional antihistamine drugs (such as diphenhydramine). Histamine effects blocked by conventional antihistamines are thought to be mediated by H_1 receptors on cell membranes; effects blocked by cimetidine are mediated by H_2 receptors[44] (Table 8). This is analogous to the alpha and beta adrenergic blocking drugs.

A prominent H_2-mediated effect is gastric acid secretion. Cimetidine inhibits all the commonly

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TABLE 8.—*H_2-Receptor Mediated Histamine Effects*

Gastric acid secretion
Atrial contraction
Relaxation of the pregnant uterus
Inhibition of cytolysis by T lymphocytes
Arteriolar dilatation
? Intrinsic factor secretion
? Others to be discovered

tested stimulants of gastric acid secretion. In patients with duodenal ulcers, 400 mg four times a day produced a 67 percent reduction in mean 24-hour gastric acidity.[45]

Preliminary data, largely uncontrolled or unpublished as of April 1976, indicate that cimetidine or metiamide (another H_2-blocker) is effective in healing duodenal and gastric ulcer, and in stopping bleeding from "stress" ulceration.[46-48]

Side effects from cimetidine have not yet been reported. Metiamide produced small, but worrisome, increases in serum transaminases and creatinine levels in about 25 percent of patients with duodenal ulcers during four weeks of therapy.[46] Metiamide produced agranulocytosis in seven patients, with one death from subsequent sepsis in a patient with systemic mastocytosis.[49] The bone marrow toxicity is thought to be related to the thiourea moiety in metiamides's structure, rather than to an H_2-receptor effect, and thiourea is not present in cimetidine. Evidence supporting the thiourea as the cause of the agranulocytosis includes (1) thioureas are known to cause agranulocytosis; (2) in contrast to metiamide, no bone marrow depression occurred in chronic toxicity tests with cimetidine in animals; (3) one patient in whom agranulocytosis developed during metiamide therapy was switched to cimetidine, and the agranulocytosis disappeared.

The effects of long-term blockage of H_2-receptors are unknown (Table 8). Additional H_2-receptors may be discovered. These facts indicate the need for caution in undertaking chronic treatment with cimetidine.

Both cimetidine and dm E_2 are effective in notably reducing acid secretion in patients with Zollinger-Ellison syndrome. These drugs may be useful in chronic treatment of some of these patients.

Bismuth

Tri-potassium di-citrato bismuthate (TDB) is a colloidal bismuth compound under investigation abroad for ulcer treatment.[50] Its mechanism of action is uncertain; the current hypothesis is that the bismuth chelates with proteins in the ulcer base, somehow promoting healing.[50] The bismuth is apparently not absorbed from the gastrointestinal tract.[50]

Preliminary results are encouraging. Increased healing rate (judged by endoscopy) and symptom relief have been reported for both duodenal and gastric ulcer in controlled trials.[50] The drug has no known toxicity.

In summary, cimetidine is the experimental drug apparently closest to release for general use in ulcer therapy in the United States. While it will probably be found effective in healing ulcers, its toxicity remains to be determined. TDB seems more promising because its potential for toxicity appears to be less; however, it is not now under investigation in the United States. Carbenoxolone and dm E^2 are, in this reviewer's opinion, of limited potential value because of their side effects.

Cimetidine and perhaps dm E_2 may prove of value in treating Zollinger-Ellison syndrome. Cimetidine is now available for experimental use in this condition.

DR. MEYER: We have just heard that traditional medical therapy of ulcer disease is directed at reducing acidity. Such an approach, while intuitively rational, lacks proven effectiveness. More effective agents are therefore being sought and tested. However, an alternative to pharmacotherapy is surgical treatment of ulcer disease. In the second half of this symposium we will consider surgical therapy. Since most ulcer patients are operated upon because their disease is considered to have been refractory to medical treatment, Dr. Grossman will open the discussion of surgical treatment by trying to define intractability for us. Dr. Passaro will indicate for us what factors influence a surgeon in choosing a particular operation for an ulcer patient, and I will close the symposium with a discussion of the outcome of surgical treatment.

MORTON I. GROSSMAN, MD, PH D:* The dictionary defines intractability, in the medical sense, as "unresponsiveness to treatment." Use of the word implies that an effective treatment for the disease in question is available but that the treatment fails in a certain fraction of patients who are therefore said to have intractable disease. None of the conventional medical treatments of duodenal ulcer

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have been shown to be more effective than no treatment at all; yet, the term intractability is frequently applied to patients with this disease, particularly in relation to indications for surgical operation. More than half of the patients who receive elective surgical treatment for duodenal ulcer have intractability listed as the primary indication for the operation.

We are caught in a kind of semantic trap. Having adopted intractability as the major criterion for elective surgical operation in duodenal ulcer, we then proceed to justify this by stating the case in terms of response to therapy. Since we have no convincing evidence that medical treatment alters the short-term or long-term course of duodenal ulcer disease, we should not use response to such treatment as the major criterion for whether or not to offer surgical treatment to the patient.

For example, some current gastroenterology textbooks state the opinion that a patient with a duodenal ulcer must fail a test of medical treatment while in hospital before being offered the surgical option. During medical-surgical conferences at which elective surgical operation for duodenal ulcer is being discussed, remarks such as the following are frequently heard: "Although this patient has had severe symptoms from his ulcer for more than half the time during the past two years, he has never had a regimen of strict medical therapy during hospitalization and therefore should not be offered surgical therapy until this has been tried." I know of no evidence that the outcome of such a test of medical therapy has value in predicting the future course of the disease and I am therefore not inclined to place very much weight on it.

If intractability is not a valid criterion for selecting patients for surgical therapy, how should this decision be made? I believe that severity of the disease is the proper criterion. The question to be answered is the following: Is this patient's duodenal ulcer disease sufficiently severe to warrant taking the risks that accompany surgical treatment (death, recurrence, side effects of operation and dollar cost)? In weighing risks against benefits in this situation, the risks are relatively fixed and known but the possible benefits—namely, the degree of relief that may come from getting rid of the symptoms—is a function of the severity of those symptoms. So we try to answer another question: Are the symptoms in this patient sufficiently severe that the chance of abolishing them warrants the risks of the operation?

TABLE 9.—*Indices of Severity*

Frequency and intensity of pain
Special symptoms: Night pain, back pain, vomiting, etc.
Antacid consumption
Loss of time from work
Admissions to hospital
Complications: documented or suggested by symptoms

If, as I propose, severity is to replace intractability as an indication for elective surgical treatment in duodenal ulcer, we must develop and perfect quantitative indices of severity. Table 9 shows some of the items that might be used for this purpose. Frequency and intensity of pain are the prime indices. We are now beginning to learn how to record information about frequency and intensity of pain in a quantitative and reproducible fashion: During how many hours of the past day was your pain present? How many days of the past week? How many weeks of the past year? How many years of the past decade? Was the pain severe enough to interfere with your activities? Special symptoms such as night pain, back pain, vomiting and others should be separately recorded. Antacid consumption can be a useful index of severity and is readily quantitated. Loss of time from work is an important quantitative index of severity, as are numbers of admissions to hospital.

The complications of duodenal ulcer—including bleeding, impaired gastric emptying, perforation and penetration into adjacent organs—sometimes require emergency surgical procedures but if not they are then usually regarded as separate indications for elective surgical treatment. Ideally, we should combine all of these indices into a single quantitative assessment of severity. This, of course, requires a system of quantification and weighting that is not now available.

I believe three steps are needed to make the choice of surgical therapy more rational. First is improved nosology. We must define quite precisely what it is that we mean by duodenal ulcer disease and its various manifestations. Because of the laxity of our present definitions of the various forms of duodenal ulcer disease, some patients get operations for duodenal ulcer even though they do not have that disease. Second, as I have indicated above, we must improve our ability to grade severity and express it in numbers. And finally we must apply decision theory[51] to help us and the patient decide whether the disutility of his symptoms and other manifestations of his dis-

ease are greater than the disutility associated with the risks of operation.

EDWARD PASSARO, JR, MD:* In substituting the concept of severity for intractability, Dr. Grossman is trying to get away from the idea that the patient has somehow failed. I would submit, however, that there are two problems wih this new concept. First, suppose a patient has just had his second episode of symptomatic ulcer disease. His having had a second uncomplicated episode probably would not be considered as indicative of severe ulcer disease. Yet under these circumstances the patient may say: "That's enough; I want my ulcer out." Dr. Grossman, how would your scheme take into consideration the patient's feeling that he has an intractable disease? Second, neither severity nor intractability can be assessed independently of developments in surgery. Suppose, for example, that a new operation is devised that is curative, and has zero mortality and zero morbidity. Then the amount of severity or intractability required for recommending surgical operation would be lessened.

DR. GROSSMAN: Let me answer your second point first. Obviously we are talking about the benefit to risk ratio. Lowering the risks improves the benefit to risk ratio so that the degree of severity (or conversely the amount of benefit to be realized by the surgical eradication of the disease) needed for recommending surgical operation is reduced proportionally.

In regard to your first point you assume that the patient does not get his word in because his physicians are doing the evaluating of the severity of his condition. That assumption is not necessarily correct. In evaluating the benefit to risk ratio, ideally the statements and desires of the patient would always be taken into account in such a formulation. Factors such as time lost from work and time required in hospital because of ulcer symptoms can be weighted in accordance with how important this lost time is to the patient. In so doing, the patient's views are incorporated into severity assessments.

DR. PASSARO: There is a constant attempt to improve the results of surgical treatment for duodenal ulcer disease. Techniques to improve results have included a retrospective analysis of past surgical experience and development of operations designed to reduce some of the sequelae of surgical operation on the stomach.

This discussion focuses on the past experience with operations for duodenal ulcer disease and the circumstances under which one operation is favored over another. Each indication for operative intervention must be considered separately as they vary greatly in their frequency, mode of treatment and results.

One of the problems in making such an assessment is that ulcer disease may not be one disease but a group of diseases so that those operated upon for one complication may have a different clinical history and outcome than the others.

Also, most patients are operated upon for intractability, currently a subjective indication; assessment of the outcome of surgical treatment in them is most often also subjective. Surgical operation carried out for objective complications (such as bleeding, perforation or obstruction), on the other hand, can be judged by the cure or prevention of these complications.

Intractability

Most patients (70 percent) referred to the surgeon for treatment have pain which is considered to be intractable—that is, patient and physician agree that further medical therapy is not warranted. Intractability, however, is a subjective assessment so that in this situation indications for surgical operation are relative, not absolute. This has prompted surgeons to do operations having the lowest incidence of undesirable side effects. Truncal vagotomy and pyloroplasty has been the most frequently employed operation because it can be done expeditiously by most surgeons (reducing the risk of operation) and because it is effective in 60 to 80 percent of patients. Its drawbacks have been twofold: the occurrence of diarrhea or dumping in 1 to 5 percent of patients and recurrent ulcer formation in approximately 10 percent. These two deficiencies have been attributed respectively to the effects of vagotomy on the small bowel and antrum and to an inadequate vagotomy. For these reasons surgeons in Europe have developed a technique to sever vagal branches innervating the parietal cell area of the stomach while sparing vagal branches to the antrum and the remainder of the gastrointestinal tract. Early results from prospective studies conducted abroad indicate this highly selective form of vagotomy (or parietal cell vagotomy) is as effective in curing duodenal ulcer disease as trun-

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cal vagotomy, but the incidence of postoperative diarrhea and dumping have been significantly less. Studies are now being prepared to assess this operation in patients in the United States.

Perforation

While the incidence of perforation is low (1 percent), this complication does not usually escape medical recognition. Because of this, there is better information on the incidence and natural history of this complication of peptic ulcer disease than of others.

Surprisingly, the mortality for ulcer perforation is only about 4 percent. This is due in part to the fact that in perforation the peritonitis is chemical rather than bacterial and the dramatic symptoms this produces cause the patient to seek prompt medical care. In addition, the low mortality is a result of advances in anesthesia and the treatment of shock.

There is considerable debate as to the most effective surgical treatment for a perforated duodenal ulcer. The more conservative group argues that taking care of the immediate problem—peritonitis—is the prime consideration and that definitive treatment can be reserved for later. Therefore, simple closure of the ulcer suffices. An elective operation can be done later with less risk in those patients in whom ulcer symptoms recur (30 to 50 percent).

The other group considers the number of patients in whom definitive treatment is required later to be excessively high. They argue that if at operation the peritoneal soilage is not excessive, and the patient has a previous history of ulcer disease, a definitive operation such as vagotomy and pyloroplasty should be done. In these selected patients there has been no increase in the mortality and morbidity.

Bleeding

Bleeding is the most serious complication of ulcer disease, with a mortality of 10 to 40 percent. Despite the extensive experience with this problem (bleeding is the reason for operating in about a quarter of the patients in whom surgical operation is done), data on the effectiveness of operations and the optimum timing for the operation are lacking and may not be obtainable.

Vagotomy and resection has had the lowest ulcer recurrence rate of any procedure and for this reason has been extensively used to treat bleeding ulcers. Because of the higher operative mortality rate with this operation compared with vagotomy and drainage procedures (especially in emergency situations), vagotomy and drainage in conjunction with ligature of the vessel has been increasingly advocated. It must be realized, however, that the initial lower mortality rate may be offset by an increased incidence of rebleeding among those in whom a vagotomy and drainage procedure has been done (there is recurrence in 2 to 25 percent—average 10 percent—of patients).

Obstruction

Patients with obstruction usually benefit most from surgical treatment of duodenal ulcer disease. Their problem of incomplete gastric emptying can usually be relieved by some mechanical aid to drainage, such as vagotomy and antrectomy or vagotomy and drainage. The latter is generally reserved for elderly, notably debilitated patients in whom a gastric resection would be unduly hazardous. There are no data to substantiate the choice of one operation over the other.

In summary, it is apparent that operation for duodenal ulcer disease continues to evolve. Surgical treatment appears to be safer and increasingly effective with fewer side effects. Barring the development of drugs capable of controlling the ulcer process, surgical operation will continue to be the definitive therapy.

DR. MEYER: Surgical treatment of peptic ulcers must be assessed by asking (1) how effective is the treatment in curing or ameliorating the disease and (2) what undesirable side effects arise from this form of treatment. As with most treatments, information provided in the world's literature bearing on these questions is incomplete, often retrospective, and poorly controlled. The bulk of this literature describes the results of surgical therapy for duodenal ulcer disease which will therefore be the focus of this review.

Effectiveness in Curing Ulcer Disease

How frequently does ulcer disease recur after surgical operation for duodenal ulcer? Recurrence rates vary with the type of operation (Figure 1).

Let us first consider truncal vagotomy with either pyloroplasty or gastroenterostomy, so-called truncal vagotomy with "drainage." Few data are available indicating recurrences over a time span of more than five years. Nobles[52] who followed 104 private patients for more than ten years after

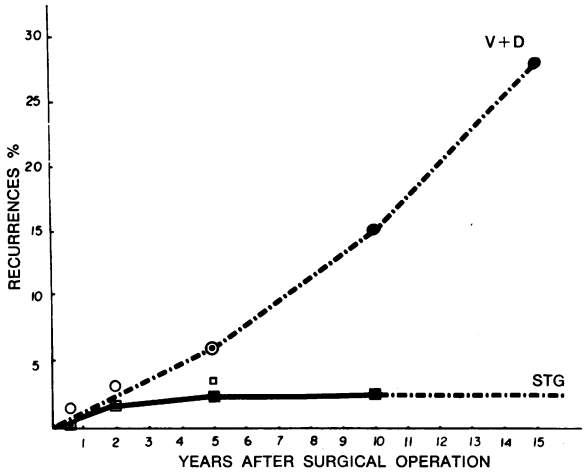

Figure 1.—Percentage of observed recurrences with time after operation. In this figure and in the tables the designation V+D refers to truncal vagotomy and drainage (pyloroplasty or gastroenterostomy), STG indicates subtotal (75 percent) gastrectomy and V+A signifies truncal vagotomy and antrectomy (distal or 50 percent gastrectomy). Closed circles are follow-up data of Nobles after V+D in his private patients; open circles are similar data after V+D among patients in the Veterans Administration's cooperative study.[53] Shaded rectangles are data from follow-up of private patients by McKeown;[55] unshaded rectangles are similar data from the Veterans Administration's cooperative study. Data indicate frequency of ulcer recurrence for the first five postoperative years is identical among private or institutional patients in whom the same operations were done.

operation observed the steady accumulation of recurrences with no fewer than 28 percent of the patients having had an observed recurrence by 15 years after operation. Nobles' observations are corroborated by other studies. In the Veterans Administration's cooperative study[53] the accumulation of observed recurrences in the first five postoperative years conforms almost exactly to the data of Nobles. Stempien's follow-up of patients operated upon at the Long Beach Veterans Administrations Hospital[54] depicted a crude recurrence rate similar to the one shown here, with 25 percent of patients followed for 15 years or more after operation having had an observed recurrence. In none of these studies was the rate of recurrence adjusted for the diminishing number of patients at risk who were followed beyond ten years postoperatively, so that the statistical risk of recurrence is poorly defined but appreciable. Although the recurrence rate after vagotomy is lower than in medically treated ulcer disease, it is disappointing in view of the expected chronic morbidity from this operation (see below).

Recurrence after subtotal gastrectomy is much less common. Again the longest recorded follow-up comes from the private-patient series of McKeown,[55] who followed 800 of his patients for a minimum of ten years after subtotal gastrectomy. We see that the recurrence rate in his study was low (2.6 percent), with all recurrences observed within the first six years after operation (Figure 1). In support of his figures, the Veterans Administration's cooperative study[53] recorded recurrences in 3.7 percent of patients by the end of the fifth postoperative year. After vagotomy plus antrectomy, recurrences are infrequent (0.7 percent) whether at five years in the Veterans Administration's cooperative study[53] or over a considerably longer period of follow-up in Herrington's personal series[56] operated upon at Vanderbilt University. We can conclude from such data that after resective surgical treatment for ulcers —whether done in institutions or private clinics —ulcer recurrence is infrequent and considerably less frequent than after vagotomy with drainage.

The above data bear on ulcer recurrence after elective surgical operation for duodenal ulcer, usually for so-called intractable ulcer disease. Another way of judging the effectiveness of surgical operations for ulcers is to examine how well such operations prevent a complication of ulcer disease which served as the indication for operation. For example, one might ask how well operation for bleeding ulcer disease prevents recurrent hemorrhage. A recent review of this problem[57] indicated that subtotal gastrectomy for hemorrhage associated with ulcer disease frequently—in 5 to 40 percent of cases—failed to prevent recurrent hemorrhage that usually appeared within five years of the index bleed. In most, but not all, of these reports, medically-treated patients rebled nearly twice as often as those treated surgically. Nevertheless, the frequent failure of subtotal gastrectomy to prevent rebleeding is in sharp contrast to low ulcer recurrence rates after subtotal gastrectomy for nonbleeding duodenal ulcers (above). This paradox is further underscored by a lower reported incidence of rebleeding after vagotomy with drainage,[58] an operation clearly inferior to subtotal gastrectomy in the prevention of nonbleeding recurrent ulcer disease (see above). Two reasonable explanations of this paradox might be that (1) ulcer disease in which bleeding occurs somehow differs from ulcer disease in which there is no bleeding, an explanation favored in the literature, or (2) significant numbers of patients with ulcer disease selected for surgical treatment for bleeding were actually bleeding from

other lesions. Either explanation underscores Dr. Grossman's earlier plea for improved nosology in the description of ulcer disease (see above). Because the two other complications of ulcer disease (perforation and obstruction) are much less common, there is scant information detailing how effective surgical operation for these complications is in preventing recurrence of the complication. Definitive surgical treatment for perforation in ulcer disease is apparently effective in preventing not only reperforation but also an otherwise virulent course of chronic ulcer disease after perforation.

In summary, surgical therapy appears more effective in treating virulent ulcer disease than medical therapy. Arguments for the merits or demerits of surgical treatment must hinge on whether the greater effectiveness of this approach is outweighed by postsurgical morbidity or mortality.

Adverse Effects of Surgical Treatment

Operative mortality for elective surgical treatment of ulcer disease is low, about half as frequent as that encountered 15 years ago.[52-56] Emergency surgical operation for hemorrhage carries a variable but considerably higher operative mortality rate. In patients surviving operation there continues to be a long-term mortality rate slightly higher than that in a control population,[59,60] but it is about the same as in medically treated, unoperated patients with ulcer disease. In short, the slight excess mortality from elective surgical therapy is not a serious deterrent for undertaking this form of treatment in virulent ulcer disease.

Rather, it is the likelihood of chronic morbidity from ulcer surgery that remains the principal deterrent to surgical treatment. Both proponents and opponents of surgical treatment acknowledge such surgically-induced morbidity but argue over its prevalence and its severity. Indeed, it is difficult to describe and quantitate the various types of postsurgical difficulties because such descriptions depend upon the subjective response of the patient as well as upon the development of a standard system of recording which would allow comparisons.

In the past 15 years, several institutions[53,61-63] have undertaken prospective trials, using randomly selected patients, of various types of ulcer operations in an effort to create a standard system of evaluation and thereby circumvent the above difficulties. The results of these various studies have been remarkably similar in two respects. First, as already noted, all studies have indicated that vagotomy with drainage is consistently inferior to resective operations with respect to ulcer recurrence, an easily quantitated form of chronic postoperative morbidity. Second, within any one study the incidence of unwanted sequelae such as subjective disability has been similar, regardless of the operation. For example, subjective dysfunction, need for restricted diet to avoid gastrointestinal symptoms, patient dissatisfaction and occupational disability were experienced with equal frequency[53] among significant numbers of patients regardless of the type of operation assigned in the Veterans Administration's cooperative study (Table 10).

Despite these fairly consistent findings within studies, there are unresolved discrepancies among studies which foment continuing debates as to the merits and demerits of surgical therapy for ulcer disease. For example, in contrast to the result of the Veterans Administration study,[53] Kiefer's[64] long-term evaluation of 550 private patients in whom subtotal gastrectomy had been carried out indicated that in only 12 percent were dietary restrictions required and that occupational disability occurred in only 9 percent. It is unresolved whether such striking differences are due to (1) inadequacies in assessment or (2) sociocultural differences between institutional and private patients. Even when results are pooled from many studies in an attempt to average out differences in methods of assessment, striking discrepancies remain. For example, dumping (postcibal abdominal distress with vasomotor symptoms) and diarrhea (more than three bowel movements per day) remain less common in private than institutional patients (Table 11).

We believe these discrepancies in subjective response to surgical operation for ulcer disease among private versus institutional patients arise from socioculturally determined[65,66] variations in perceptions of postsurgical dysfunction. For example, whether or not they were symptomatic, all patients operated upon for ulcers when studied in detail have been found to have profound alterations in alimentary processes as the result of operation.[67,68] Consequently, the better subjective result in private patients is not necessarily evidence that such surgical treatment is free of physiological detriment.

A clinical illustration of this argument (that in many patients, private or institutional, sympto-

TABLE 10.—*Frequency of Subjective Complaints Among Institutional Patients Five Years After Surgical Operation for Ulcer Disease**

	V+D (208 pts) (percent)	V+A (210 pts) (percent)	STG (230 pts) (percent)
Impaired strength (patient's statement)	43.5	42.5	45.3
Restricted diet	37.8	39.8	43.6
Work lost	18.1	22.6	17.6
Poor to fair result (Patient's statement)	15.1	13.4	9.4

V+D signifies vagotomy and drainage
V+A is vagotomy and antrectomy
STG indicates subtotal gastrectomy

*From the Veterans Administration's cooperative study.[53]

TABLE 11.—*Frequency of Gastrointestinal Complaints Among Patients Two or More Years After Surgical Operation**

	V+D (percent)	V+A (percent)	STG (percent)
Dumping	23.2 VA	29.4 VA	38.8 VA
	18.2 Univ	24.6 Univ	22.4 Univ
	12.4 Private	....	6.8 Private
Diarrhea	18.5 VA	21.6 VA	16.5 VA
	21.4 Univ	23.2 Univ	6.5 Univ
	16.2 Private	....	....

V+D signifies vagotomy and drainage
V+A is vagotomy and antrectomy
STG indicates subtotal gastrectomy

*Comparisons are made between institutional and private patients with published data from two Veteran Hospital studies (VA),[50,59] one university (Univ) study[61] and three follow-up studies of patients from private practice.[52,55,64]

matic or asymptomatic, there are significant physiological derangements as a result of operation for ulcer disease) is provided by data on the development of postoperative anemia. After such operation, many patients lose weight, and specific nutritional deficiencies develop in some which give rise to metabolic bone disease[69] or peripheral neuropathy.[70,71] Unfortunately, the literature does not describe postoperative weight loss in a standard fashion which allows statistical compilation; and the prevalence of metabolic bone disease or peripheral neuropathy varies with the application and sensitivity of methods used to assess those abnormalities. However, most clinical reports routinely describe blood hemoglobin concentrations so that extensive comparisons can be made among reports of the outcome of such surgical treatment. Following operation for ulcer disease there is a progressive decline with time in the mean blood hemoglobin concentration.

The increasing prevalence of anemia is associated with a parallel decline in serum iron, and, in some cases, in serum B_{12}, both of which are inefficiently absorbed following surgical operation for ulcers. There is no correlation between the development of anemia and the subjective symptomatic result[55,72,73] but by ten years or more after subtotal gastrectomy no fewer than 30 percent of patients[55,69,72] have anemia. Long-term evaluations of patients in whom truncal vagotomy with drainage has been done—that is, nonresective surgical operation—indicate similar prevalence of anemia and iron deficiency 15 to 20 years after operation.[74-76]

In summary, current surgical treatment is effective in curing ulcers at only slight risk of operative mortality for an elective operation. The significant prevalence of subjective, chronic morbidity and objective nutritional impairment following these operations is the major deterrent against a wider application of this form of treatment. Nevertheless, surgical therapy continues to evolve as surgeons search for new operations that combine effectiveness with a lower incidence of chronic side effects.

DR. GROSSMAN: How likely is it that a new operation, proximal gastric vagotomy, will change the outlook for patients in whom surgical therapy is required?

DR. MEYER: There are two aspects to that question: (1) how effective is this new operation in curing ulcer disease and (2) does it produce less chronic morbidity. In regard to the first aspect, there are conflicting reports after five years of trials in Europe, one group claiming ulcer recurrence in as few as 5 percent of patients and another group, in as many as 20 percent. It is my guess that the more time that elapses after proximal gastric vagotomy, the higher will be the ulcer recurrence rate—just as after truncal vagotomy. Nevertheless, we need data, not guesses. In terms of chronic postoperative morbidity (the risk side of the benefit to risk ratio), it is already apparent that this new operation is much less frequently associated with postoperative symptoms (dumping or diarrhea) or objectively measured derangements in alimentary functions. What we need are more studies to determine whether the ulcer cure rate (benefit) is high enough to recommend this operation in place of the others.

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